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ORIGINAL ARTICLE

Microwave assisted chemistry: A rapid and regioselective route for direct *ortho*-acylation of phenols and naphthols by methanesulfonic acid as catalyst

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KEYWORDS

Microwave;
Methanesulfonic acid;
Friedel–Crafts;
Ortho-*C*-acylation;
Regioselective

Abstract Direct *ortho*-acylation of phenols and naphthols with methanesulfonic acid (MSA) as the catalyst has been studied under microwave stimulation. The microwave assisted reaction was environmentally benign in terms of faster reaction, useful conditions and higher yield of the desired products. However, after 3–4 min reaction time at 200–300 Watt, selectivity to over 98% *ortho*-acylation products was obtained. These reactions have some advantages in competition with other methods such as; short reaction times, high yield and regioselectivity of products, mild reaction conditions and easy workup of the reactions.

1. Introduction

Microwave chemistry has emerged as a discipline that permits all aspects of synthetic chemistry. The major goals of this endeavor are to maximize the efficient use of safer raw materials and to reduce waste (Abramovitch, 1991; LidstroÈm et al., 2001; Polshettiwar and Varma, 2008). Orthohydroxyaryl ketones, are also important synthetic intermediates in the synthesis of biologically active compounds such as chalcones, flavanones, naphthoquinones and pesticides (Crouse et al., 1981). In the Friedel–Crafts acylation reaction by general catalysts the formation of complexes between the arylketone and the activator (catalyst) imposes the use of the catalyst in at least a stoichiometric amount or more, e.g. $AlCl_3$. Consequently, carrying out such a reaction on an industrial scale generates considerable waste. In order to solve this problem, some new catalyst for Friedel Craft acylations has recently been developed by chemists (Sartori and Maggi, 2006).

There are some reports on catalytic Friedel Crafts acylation reactions using carboxylic acids as acylating agents. In these reactions, reagents such as; zeolites (Singh and Pandey, 1997), heteropoly acids and their salts (Kaur and Kozhevnikov, 2002), clay (Chiche et al., 1987), Lewis acids (Kobayashi et al., 1996), graphite/TsOH (Kureshy et al., 2006), hydrogen fluoride (Fieser and Hershberg, 1940) and *N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine (TMEDA) (Kadam et al., 2009) have been used as catalysts. Recently, it has been found that although phenolic substrates can be converted into acylated

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compounds by means of MSA/alumina and MSA/graphite as the catalyst under reflux conditions (Sharghi et al., 2006), these methods have some limitations, such as; low yields, long reaction times, and usage of solvents in the reaction process.

MSA is a strong acid ($pK_a = -1.9$), which is almost completely ionized at 0.1 M in an aqueous solution, and has a low tendency to oxidize organic compounds. Moreover, it is, far less corrosive and toxic than the usual mineral acids. Under normal conditions aqueous solutions evolve no dangerous volatiles, making it safe to handle. Finally, it is readily biodegradable within 28 days, only forming CO_2 and sulfate, making it an environmentally benign material (Gernon et al., 1999).

2. Material and methods

Chemicals were purchased from the Merck Chemical Company in high purity. An IR spectrum was recorded as KBr pellet on a Perkin-Elmer 781 Spectrophotometer and an Impact 400 Nickolet FTIR Spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ with (250 MHz) Spectrometer using of TMS as an internal reference. Microwave-assisted reactions were performed with a Milestone *ETHOS EZ* apparatus, keeping irradiation power fixed and monitoring the internal reaction temperature. Melting points obtained with a Yanagimoto micro melting point apparatus are uncorrected. The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

2.1. Microwave procedure for acylation of phenol and naphthol derivatives

A mixture of substrate (1 mmol), aliphatic carboxylic acid (4 mmols) and 0.045 g (0.5 mmol) of methanesulfonic acid react together under microwave irradiation with 200 W for 30 s. The progress of the reaction was monitored by thin layer chromatography (TLC). After cooling to room temperature, the reaction mixture was dissolved in dichloromethane (10 ml) and washed with aqueous $NaHCO_3$ (3×10 ml), followed by H_2O (about 20 ml). After extraction, the organic phase was dried with $CaCl_2$, filtered and evaporated to give a crude product. The products were established by their spectroscopic and physical data that were consistent with previously reported data (Naeimi and Moradi, 2006a,b, 2007). The yields refer to isolated pure products after column chromatography.

2-acetyl-1-naphthol (**1**): recrystallization from a *n*-hexane/CH_2Cl_2 (15:1 v/v) mixed solvents; mp 98–100 °C; IR (KBr)/υ (cm^{-1}) 3300–3600, 1625, 1570; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.6 (s, 3H), 7.5–8.3 (m, 6H), 13.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 112.9, 117.6, 124.4, 124.6, 125.3, 126.9, 129.4, 137.6, 162.4, 202.04; MS (EI): *m*/*z*: 186, 171, 169, 127.

1-(1-hydroxy-2-naphtyl)1-propanone (**2**): recrystallization from a *n*-hexane/CH_2Cl_2 (15:1 v/v) mixed solvents; mp 84–85 °C; IR (KBr)/υ (cm^{-1}) 3330–3580, 1651, 1565; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.2 (t, 3H), 2.5 (q, 2H), 7.4–8.1 (m, 6H), 13.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 25.5, 118.1, 119.1, 126.0, 127.6, 128.1, 128.7, 131.1, 135.4, 161.8, 205.1; MS (EI): *m*/*z*: 200, 183, 171, 143, 126.

1-(1-hydroxy-2-naphtyl)1-butanone (**3**): recrystallization from a *n*-hexane/CH_2Cl_2 (15:1 v/v) mixed solvents; mp 94–96 °C; IR (KBr)/υ (cm^{-1}) 3220–3580, 1641, 1564; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.1 (t, 3H), 2.1 (m, 2H), 2.4 (t, 2H), 7.6–8.4 (m, 6H), 13.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 18.1, 51.1, 110.1, 115.0, 125.1, 126.7, 127.0, 128.5, 130.1, 133.6, 158.4, 195.0; MS (EI): *m*/*z*: 214, 171, 154, 127.

1-Acetyl-2-naphthol (**4**): purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/υ (cm^{-1}): 3200–3500, 1725, 1675; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.6(s, 3H), 7.5–8 (m, 6H), 13.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.1, 114.5, 119.0, 123.8, 124.2, 127.9, 128.6, 129.6, 131.1, 136.7, 164.1, 202.0; MS (EI): *m*/*z*: 186, 169, 155, 143, 127.

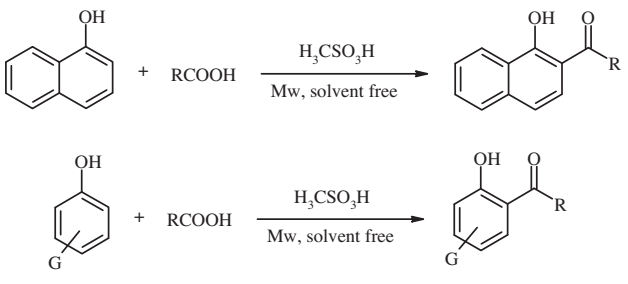
2-Hydroxy-3-methyl acetophenone (**5**): purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/υ (cm^{-1}): 3200–3500, 1650, 1600; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.2 (s, 3H), 2.6 (s, 3H), 7.5–7.8 (m, 3H), 12.1 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 28.8, 117.6, 118.2, 124.1, 128.3, 136.2, 160.7, 202.4; MS (EI): *m*/*z*: 150, 135, 119, 107, 91, 43.

2-Hydroxy-4-methyl acetophenone (**6**): purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/υ (cm^{-1}): 3200–3500, 1600, 1670; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.8 (s, 3H), 2(s, 3H), 6.2–7 (m, 3H), 11.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 27.4, 114.3, 118.9, 120.5, 129.4, 144.7, 162.4, 203.2; MS (EI): *m*/*z*: 150, 135, 133, 119, 91, 43.

2-Hydroxy-5-methylacetophenone (**7**): recrystallization from a *n*-hexane/CH_2Cl_2 (10:1 v/v) mixed solvents, mp 42–44 °C; IR (KBr)/υ (cm^{-1}): 3300–3500, 1650, 1575; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.2 (s, 3H), 2.4 (s, 3H), 6.8–7.4 (m, 3H), 11.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 27.3, 112.9, 118.2, 132.9, 134.4, 135.1, 160.3, 204.1; MS (EI): *m*/*z*: 150, 133, 119, 91, 43.

2-Hydroxy-3,5-dimethylacetophenone (**8**): purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/υ (cm^{-1}): 2900–3450, 1770–1650; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.4(s, 3H), 2.5 (s, 3H), 2.8 (s, 2H), 7.5 (d, 2H, J = 9 Hz), 12.6 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.3, 20.1, 28.4, 121.1, 124.9, 129.4, 132.4, 134.9, 156.7, 204.3; MS (EI): *m*/*z*: 164, 147, 133, 121, 105, 43.

2-Hydroxy-5-bromoacetophenone (**9**): recrystallization from a *n*-hexane/CH_2Cl_2 (10:1 v/v) mixed solvents, mp 58–61 °C; IR (KBr)/υ (cm^{-1}): 3350–3620, 1661, 1568; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.4 (s, 3H), 6.8–7.4 (m, 3H), 11.8 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.3, 116.0, 120.5, 131.0, 136.1, 137.1, 164.3, 198.0; MS (EI): *m*/*z*: 215, 200, 135, 120, 92.



Scheme 1

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1-(2-hydroxy-5-methylphenyl)-1-propanone (**12**): purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; (b.p. 123–124 °C); IR (Neat)/υ (cm^{-1}): 3200, 1720, 1620; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.0(t, 3 H), 2.0(s, 3 H), 2.6(m, 4 H), 6.5–7.2(m, 3 H), 11.9(s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 18.9, 20.4, 45.3, 114.7, 118.1, 132.5, 134.0, 135.8, 160.8, 196.3; MS (EI): *m*/*z*: 178, 161, 135, 119, 91, 71.

1-(2-Hydroxy-5-methylphenyl)-1-butanone (**13**): purified by silica gel chromatography eluted with 20:1 *n*-hexane/EtOAc as light yellow oil; IR (Neat)/υ (cm^{-1}): 3300, 1730, 1620; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.9(t, 3 H), 1.6(m, 4 H), 2.3(s, 3 H), 2.6(t, 2 H), 6.7–7(m, 2 H), 7.2(s, 1 H), 11.9(s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 22.8, 26.4, 44.1, 113.8, 118.1, 132.4, 134.0, 135.8, 160.1, 191.5; MS (EI): *m*/*z*: 192, 177, 175, 149, 91, 57.

Table 1 Catalytic acylation of phenol or naphthol derivatives with MSA using Microwave stimulation[a].

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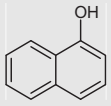
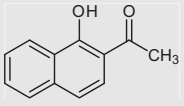
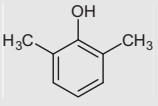
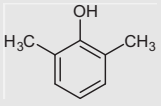
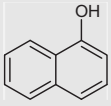
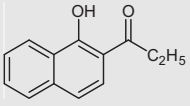
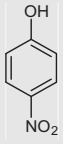
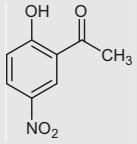
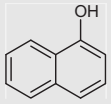
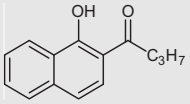
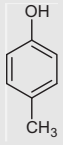
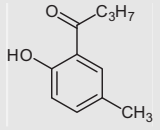
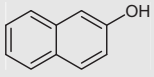
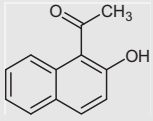
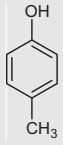
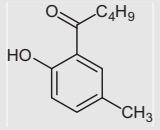
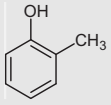
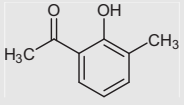
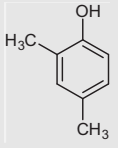
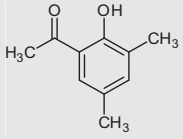
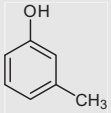
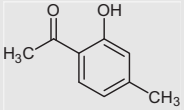
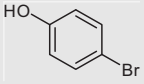
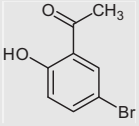
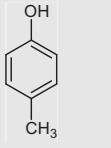
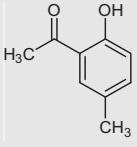
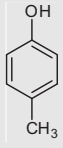
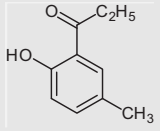
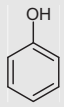
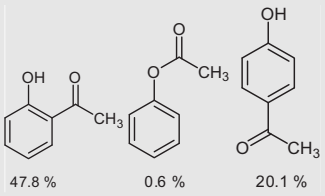
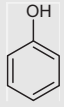
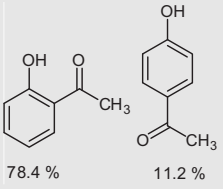
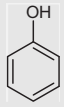
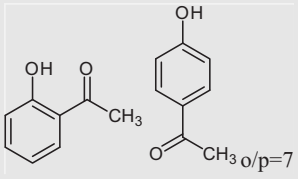
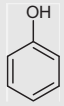
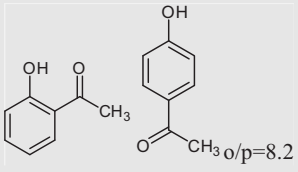
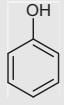
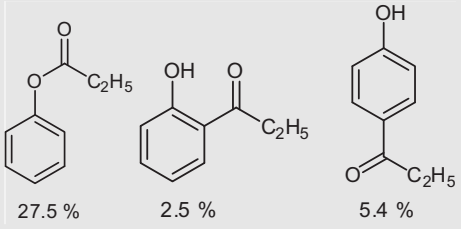
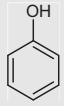
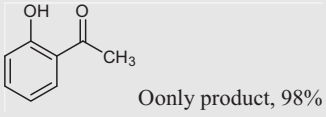
1			200 (120)	95	8			400 (10 min)	-
2			200 (120)	97	9			300 (10 min)	5
3			200 (150)	95	10			200 (180)	95
4			200 (150)	40	11			200 (180)	90
5			200 (100)	45	12			200 (200)	90
6			200 (100)	80	13			200 (200)	85
7			200 (100)	93	14			200 (180)	88

[a] For 1 mmol of substrate it used 4 mmol of aliphatic acid and 0.5 mmol of MSA.
[b] Isolated yields.

Table 2 Some previously reported methods for the acylation of phenols compared with this work.

Entry	Substrates	Conditions	Products/yields	Ref.
1		$(MeCO)_2O$, CoZSM-5 modified zeolite, 250 °C	 47.8 % 0.6 % 20.1 %	Subba Rao et al. (1995)
2		Acetic acid (g), HZSM-5	 78.4 % 11.2 %	Neves et al. (1994a)
3		Acetic acid (g), Dealumination of HZSM-5 zeolite	 o/p=7	Neves et al. (1994b)
4		Acetic acid (g), zeolite HY	 o/p=8.2	Padró and Apesteguía (2004)
5		C_2H_5COCl, Hβ or HZSM-5 zeolite, 140 °C	 27.5 % 2.5 % 5.4 %	Chaube et al. (2001)
6		H_3CCOOH, Methanesulphonic acid, microwave, solvent free	 Oonly product, 98%	–

3. Results and discussions

In this research, we have developed the microwave-assisted *ortho*-acylation of hydroxyaryl compounds with organic acids and MSA as the catalyst (Scheme 1) that was performed without solvent, to afford the corresponding *ortho*-acylated hydroxyaryl compounds, in high yields. The obtained results are indicated in Table 1.

In all cases, the acylation of these phenolic compounds was performed with acetic acid without solvent by using MSA to afford the corresponding *ortho*-acylated hydroxyaryl compounds, in high yields and short reaction times. As it can be seen from Table 1, our reported conditions are generally applicable to phenols and naphthol derivatives.

The reaction is regioselective in that *ortho*-acylated products are obtained in the most cases, except, with entry 8

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Table 3 *Ortho*-acylation of 1 mmol *p*-cresol with 4 mmol of various organic acids, in the presence of MSA as catalyst[a].

Entry	Acid	P(W)	Time (sec)	Yield[b](%)
1	CH_3CO_2H	200	100	93
2	$C_2H_5CO_2H$	200	180	88
3	$C_3H_7CO_2H$	200	180	95
4	$C_4H_9CO_2H$	200	180	90

[a] The reaction occurred in 0.5 mmol MSA under microwave conditions.
[b] Isolated yields.

(Table 1) in which two ortho positions are occupied with methyl groups and no acylated product was obtained. This sequence proved the high regioselectivity of these reactions into direct *ortho*-acylation. This regioselectivity can be related to chelating the phenolic OH with methanesulfonic acid accomplished with carboxylic acid for the formation of acylium ion. In entry 9, electron-withdrawing substituents reduce the reactivity of substrates and thus, in the high power of microwave irradiation, afforded any product.

In order to find the significance and advantages of this method over previous methods of acylation, the obtained results from our method were compared with other previously reported works (Chaube et al., 2001; Neves et al., 1994a; Neves et al., 1994b; Padró and Apesteguıa, 2004; Subba Rao et al., 1995). The corresponding comparative results are indicated in Table 2. As can be seen in this table, in our method, the only product was regioselectively obtained toward direct ortho C-acylation in excellent yield and short reaction time under solvent free conditions (entry 6, Table 2). While, the other works yielded a mixture of ortho and para C-acylated products (entries 2–5, Table 2), moreover, in another method the O-acylation product was also observed (entry 1, Table 2). Due to the above-mentioned benefits (high regioselectivity and yield product), the simplicity of the reaction process and easy work-up can be some advantages of our method than other methods.

For the development of methanesulfonic acid as the catalyst in the acylation reaction with other organic acids as acylating agents, the reaction of *p*-cresol, with acetic, propanoic, butanoic and pentanoic acids under microwave conditions was examined (Table 3). As can be seen in this table, all of the products were formed in high yields and short reaction times.

4. Conclusion

This new method for acylation of phenols and naphthols is a mild, efficient, easy and clean reaction for the preparation of ortho hydroxyaryl ketones in excellent yields with high regioselectivity into substitution of acyl group in ortho situation. The reactions have also occurred without solvent on the various phenol and naphthol derivatives with different organic acids in the presence of a lot of mild Lewis acids under microwave irradiation and atmospheric condition.

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